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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1609	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/530,056	KOGA ET AL.	
	Examiner	Art Unit	
	Walter E. Webb	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☒ Claim(s) *5 and 6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/04/2006 and 07/25/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-6 are pending.

Claims 5 and 6 are withdrawn from consideration.

Claims 1-4 are rejected.

Claim Objections

Claims 5 and 6 are objected to under 37 CFR 1.75(c) as being in improper form because multiple dependent claims 5 and 6 each depend from claim 3, which is itself a multiple dependent claim. A multiple dependent claim must be considered in the same manner as a plurality of single dependent claims. See MPEP § 608.01(n). Accordingly, claims 5 and 6 will not be further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating the expression of clinical symptoms in a disease caused by mitochondrial dysfunction, does not reasonably provide enablement for preventing the expression of clinical symptoms in a disease caused by mitochondrial dysfunction. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the breadth of the claims;

3) the predictability or unpredictability of the art;

4) the amount of direction or guidance presented;

5) the presence or absence of working examples;

6) the quantity of experimentation necessary;

7) the state of the prior art; and,

8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2: The claimed invention is drawn to a composition for preventing the expression of clinical symptoms in a disease caused by mitochondrial dysfunction, where the composition contains L-arginine as an active ingredient (claim 1).

Factors 3 and 7: In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the prevention of symptoms associated with

mitochondrial dysfunction, which exhibited some sensitivity to L-arginine in general, could be effectively achieved by the administration of the claimed active agent. Based on the state of the art, as discussed below, the artisan would have only accepted that the treatment of specific symptoms could be achieved, rather than that such an agent could have been used to prevent all known symptoms.

As set forth in In re Marzocchi et al., 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling."

Factor 4: Applicant disclosed guidance in the form of clinical studies showing that the onset frequencies of episodes and warning systems associated with mitochondrial dysfunction were decreased. Applicant also disclosed how a human or animal might be administered this composition. Still, further guidance is needed in regards to humans and animals. To enable the Artisan to reasonably predict that Applicant's composition can prevent symptoms associated with mitochondrial dysfunction, Applicant should set forth a protocol or guidance as to how prevention of

these clinical symptoms could be achieved. Applicant's disclosure is inadequate as to directing or guiding how the proposed agents can be employed to accomplish such objectives in a predictable manner.

Factor 5: The specification at pages 17-19 provides evidence demonstrating that the composition reduces the onset of frequencies of episodes and warning systems associated with mitochondrial dysfunction in patients diagnosed with MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). While the present claims encompass preventing the expression of clinical symptoms in a disease caused by mitochondrial dysfunction, Applicant's data merely establishes a decrease in the onset symptoms in patients diagnosed with MELAS. No data has been provided, or reasonable scientific basis exists, for treating such results as a prevention of symptoms associated with mitochondrial dysfunction.

Treatment of symptoms associated with MELAS, for example, is well developed (see Mandava et al., "Metabolic Disease & Stroke: MELAS." 2006: www.emedicine.com/NEURO/topic580.htm), but the state of the art with regard to preventing symptoms in general is grossly underdeveloped.

In this regard, Mandava et al. is cited. In particular, there is no known agent that is effective against preventing all symptoms associated with MELAS. The Mandava reference clearly shows that for the different symptoms associated with MELAS and the severity of the disease, there is not one agent or combination thereof that is effective at preventing every symptom (see Medical Care, pp 6-8.).

Given that there was not known a specific agent or combination of agents effective to prevent all symptoms associated with MELAS, one of ordinary skill in the art would not accept on its face Applicant's statement that such an objective could be achieved with any symptom associated with any mitochondrial dysfunction. The artisan would have required sufficient direction as to how to predict what particular types of symptoms associated mitochondrial dysfunction would actually show sensitivity to the presently claimed composition such that the artisan would have been imbued with at least a reasonable expectation of success in preventing such symptoms. Such success would not have been reasonably expected for preventing symptoms associated with mitochondrial dysfunction given the variable nature of mitochondrial dysfunction known in the art. The prevention of symptoms associated with MELAS, for example, would have been an outcome not reasonably expected by one of ordinary skill in the art. To the artisan, the concept of a single agent, or even a combination of agents, that is effective to prevent symptoms associated with mitochondrial dysfunction in a mammal would have been unique and, thus, met with a great deal of skepticism.

The Examiner acknowledges that the Office does not require the presence of working examples to be present in the disclosure of the invention (see MPEP §2164.02). However, in light of the state of the art, which recognizes the unpredictable nature of treating MELAS, there is no apparent disclosure to support the contention that an symptoms associated with mitochondrial dysfunction can be prevented by simply administering, by any method, an L-arginine composition, since the present

specification fails to enable one of ordinary skill in the art to practice the entirety of the presently claimed invention.

Factor 6: The burden of preventing symptoms associated with mitochondrial dysfunction in a mammal with the claimed composition is much greater than that of treating specific symptoms associated with mitochondrial dysfunction in a mammal, with specific types of compounds. Since the present specification would not enable the skilled artisan to prevent symptoms associated with mitochondrial dysfunction in a mammal with the claimed composition, a clear burden of undue experimentation would be placed upon the skilled artisan in order to practice the full scope of the presently claimed invention.

Factor 8: In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that preventing symptoms caused by mitochondrial dysfunction in a mammal with the claimed composition could be achieved. In order to actually achieve such an objective, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize, and Applicant as failed to demonstrate, via direct evidence or sound reasoning, that symptoms caused by mitochondrial dysfunction can

be prevented with the claimed composition, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 1-6 are deemed properly rejected.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular applicant has not adequately described "clinical symptoms in a disease caused by mitochondrial dysfunction" of claims 1-2, and "warning symptom thereof" of claim 3.

Claims 1-4 are drawn to a composition for preventing and/ or treating the expression of clinical symptoms in a disease caused by mitochondrial dysfunction containing L-arginine (claim 1), where L-arginine is orally administered in an amount from 1-30 g a day per adult (claim 2), where the mitochondrial dysfunction is a cerebral apoplexy-like episode of MELAS or a warning symptom thereof (claim 3), where the warning symptom is scintillating scotoma (claim 4).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics,

structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, applicant discloses that scintillating scotoma is a warning symptom and that clinical data showed a decrease in convulsions after patients were administered L-arginine. There is no description of these phrases in the specification such that one of ordinary skill in the art would reasonable discern what is meant by "clinical symptoms in a disease caused by mitochondrial dysfunction" and "warning symptom thereof." The clinical tests at pages 17-19 are inadequate for discerning the meaning of the full breadth and scope of these phrases. Therefore, a "clinical symptoms in a disease caused by mitochondrial dysfunction" and "warning symptom thereof" are not supported in the specification. Because of this lack of support, it is not clear that applicant had possession of the claimed invention at the time of filing.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See Vas-Cath at page 1116). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v.Revel, 25USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai

Pharmaceutical Co. Ltd., 18USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Cooke et al., (US 5,891,459).

Applicant claims a composition for preventing and/ or treating the expression of clinical symptoms in a disease caused by mitochondrial dysfunction containing L-arginine (claim 1), where L-arginine is orally administered in an amount from 1-30 g a day per adult (claim 2), where the mitochondrial dysfunction is a cerebral apoplexy-like episode of MELAS or a warning symptom thereof (claim 3), where the warning symptom is scintillating scotoma (claim 4).

Cooke teaches a method of improving vascular nitric oxide activity by orally administering L-arginine or L-arginine hydrochloride (see claim col. 26 lines 38-50, or claim 1). Cooke also teaches a method where a cereal bar includes a mixture of L-arginine, L-lysine (another nitric oxide-releasing agent), and Vitamin C (see claim 15,

col. 28 lines 20-30.) Cooke disclosed an example of the effects of its composition after oral administration of L-arginine at 7g per day per adult for 2 weeks (see col. 22 lines 40-50).

Regarding claims 1-4 claiming a composition for preventing and/ or treating the expression of clinical symptoms in a disease caused by mitochondrial dysfunction, it is well settled that the recitation of a new intended use for an old product does not make a claim to that old product patentable. See In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("The discovery of a new property or use of a previously known composition, even when that property and use are unobvious from prior art, can not impart patentability to claims to the known composition."); Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 782,227 USPQ 773, 778 (Fed. Cir. 1985) (composition claim reciting a newly discovered property of an old alloy did not satisfy section 102 because the alloy itself was not new); In re Pearson, 494 F.2d 1399, 1403, 181 USPQ 641,644 (CCPA 1974) (intended use of an old composition does not render composition claim patentable). The intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Since the L-arginine composition of Cooke is capable of performing the intended use of preventing and/ or treating the expression of clinical symptoms in a disease caused by mitochondrial dysfunction, then it meets the claims.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Ashina et al., The Lancet 1999, which discusses the effect of L-

arginine on chronic tension headache; Moskowitz (US 5385940), which discusses treatment of stroke with nitric oxide releasing compounds.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 9:00am-5:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

9/1/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

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